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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,838	10/14/2005	Nobutaka Fujii	FUJII8	2131

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,838	FUJII ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7-10,14,15,17,18,23-35 and 39-45* is/are pending in the application.

4a) Of the above claim(s) *3,5,7-10,14,25-32,35,39,40 and 42-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,15,17,18,23,24,33,34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restriction filed on May 25, 2007 is acknowledged. New claims 41-45 have been added. Claims 1-3, 5, 7-10, 14-15, 17-18, 23-35 and 39-45 are pending in this application.

Restriction

1. Applicant's election with traverse of Group I (claims 14, 31-32 and 18 and 39) drawn to a pharmaceutical composition comprising a peptide with the formula X-DLys-Pro-Tyr-Arg-Cit-Cys-Arg, and a method for preventing or treating chronic rheumatoid arthritis in subjects by administering to the subject a pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a peptide and the election of SEQ ID NO: 64 in the reply filed on May 25, 2007 is acknowledged. The traversal is on the ground(s) that the unifying technical feature shared among the peptides of the invention resides in their common, novel N-terminal derivatiziation and/or specific substitutions, and not in their C-terminal half on which the Examiner has focused on. In addition, the peptides also share a common secondary structure, hence different peptide species described by the Examiner as "distinctive inventions" rather derive from a common inventive concept, namely that of T-140 peptide analogs with the specific derivatization at the alpha-amino nitrogen and/or particular amino acid substitutions. Furthermore, the Applicants argue that Group 1 combines composition and method claims, it would be proper to rejoin Groups 10-17 with Group 1 (since the "species" of treating cancer is being elected below). This is not found persuasive

because the peptides are considered having a common primary structure, and not dependent on secondary structures. Many proteins have the same secondary structures when folded, but have very different primary structures (amino acid sequences). A national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) a product and a process specially adapted for the manufacture of said product; or

(2) a product and a process of use of said product: or

(3) a product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) a process and a apparatus specifically designed for carrying out said process; or

(5) a product, a process specially adapted for the manufacture of the said product and an apparatus specifically designed for carrying out said process. 37 CFR 1.475.

The species election of different diseases and CXCR4 antagonist was done in error, thus, the species election of different diseases and CXCR4 antagonist is being withdrawn. The species election of SEQ ID NOS: 11-68 is maintained.

Please note: It appears that the Applicants are claiming that the species of the peptides are not patentably independent and distinct, due to the same secondary structures. If this is indeed the case, the Applicants are reminded to please put this in writing. Additionally, the Applicants are reminded of "**should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be**

obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species."

2. The requirement is still deemed proper and is therefore made FINAL. Claims 1-3, 5, 7-10, 15, 24-30 and 17, 34-35 and 40 are linking claims to Group 1. Claim 41 is withdrawn from further consideration as being drawn to a nonelected Invention. Claims 5, 7-8, 10 and 26-28 are withdrawn from further consideration as being drawn to a nonelected species. A search was conducted on the elected species, SEQ ID NO: 64, and it appears to be free of the prior art. The search was extended to include the core sequence DLys-Pro-Tyr-Arg-Cit-Cys-Arg and this too appears to be free of prior art. The search was extended to include the broad Markush claim of claim 1. Claims 3, 9, 14, 25, 29, 30, 31, 32, 35, 39, 40 and 42-45 are further withdrawn from consideration being drawn to nonelected species and invention. Claims 1-2, 15, 17, 18, 23-24 and 33-34 are examined on the merits in this office action. Please note: elected species appear to be free of the prior art. However, the claims encompassing the elected species consist of other species that are not elected. Thus, those claims consisting of the elected species have been withdrawn from further consideration.

Priority

3. This application is a 371 of PCT/JP03/10753, filed August 26, 2003 and priority to foreign document JAPAN 2002-247843, filed August 27, 2002. A certified copy of the

foreign document has been received and entered. Thus, the Application is given priority to August 27, 2002.

Rejection-35 U.S.C. 112, 1st

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 17-18 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention aims at providing a novel means using CXCR4 antagonisttic compounds for the prevention and/or therapy of cancers and rheumatoid arthritis in subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a peptide.

(2) The state of the prior art:

In regards to "preventing a cancers", Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting, neuropathy, nausea, anorexia, seizures, hypercalcemia, hyperuricemia, or obstruction...Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis).

Furthermore, arts indicate the difficulties in going from *in vitro* to *in vivo* for drug development for treatment of cancers. Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic resonse. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants...*In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test sites are not typical of the *in vivo* reality (see p. 167, left column, 1st paragraph). Gura T (Science, 1997, 278(5340): 1041-1042, encloses 1-5) indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (see p. 1, 2nd paragraph). Furthermore, Gura T indicates that the results of xenograft screening turned out to be not much better than those obtained with the original models, mainly because the xenograft rumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues, for example (see p. 2, 4th paragraph). Further, when patient's tumor cells in Petri dishes or culture flasks and monitor the cells' responses to various anticancer treatments, they don't work because the cells simply fail to divide in culture, and the results cannot tell a researcher how anticancer drugs will act in the body (see p. 3, 7th paragraph). Furthermore, Jain RK (Scientific American, July 1994,58-65) indicates that the existing pharmacopoeia has not markedly reduced the number of deaths caused by the most common solid tumors in adults, among them cancers of the lung, breast, colon, rectum, prostate and brain (see p. 58, left most column, 1st

paragraph). Further, Jain RK indicates that to eradicate tumors, the therapeutic agents must then disperse throughout the growths in concentrations high enough to eliminate every deadly cells...solid cancers frequently impose formidable barriers to such dispersion (see p. 58, bottom of the left most column continuing onto the top of the middle column). Jain RK indicates that there are 3 critical tasks that drugs must do to attack malignant cells in a tumor: 1) it has to make its way into a microscopic blood vessel lying near malignant cells in the tumor, 2) exit from the vessel into the surrounding matrix, and 3) migrate through the matrix to the cells. Unfortunately, tumors often develop in ways that hinder each of these steps (see p. 58, bottom of right most column). Thus, the art recognizes that going from *in vitro* studies to *in vivo* studies for cancer drug developments are difficult to achieve.

In regards to "a method for preventing or treating chronic rheumatoid arthritis", The Merck manual indicates that rheumatoid arthritis (RA) is a chronic autoimmune disease producing damage mediated by cytokines, chemokines, and metalloproteases. Peripheral joints are symmetrically inflamed, often resulting in progressive destruction of articular structures. Diagnosis requires specific clinical, laboratory, and radiologic criteria. Treatment involves drugs, physical measures, and sometimes surgery (see Merck manual, Rheumatoid Arthritis). Further, the Merck manual indicates that although RA involves autoimmune reactions, the precise cause is unknown, many factors may contribute, such as genetic predisposition, unknown environmental factors (e.g., viral infections) and cigarette smoking (see Merck manual, RA, Etiology and Pathophysiology). Further, the Merck manual indicates that the onset of symptoms is

usually insidious, beginning with systemic symptoms and progressing to joint symptoms, but symptoms can occur simultaneously (see Merck manual, RA, 1st paragraph, Symptoms and Signs). For diagnosis, patients should have a RF test, hand and wrist x-rays, and baseline x-rays of affected joints to document future erosive changes (see Merck manual, RA, 1st paragraph, Diagnosis). Furthermore, the Merck manual indicates that treatment involves a balance of rest and exercise, adequate nutrition, physical measures, drugs, and sometimes surgery. Drugs used are to reduce inflammation as means of preventing erosions and progressive deformity. Many promising new drugs that appear to slow the progression of RA are available (see Merck manual, RA, Treatment and Drugs for RA).

The art provide guidance as to how to treat cancers and reduce the progression of RA, but do not provide guidance as how to how to determine individuals who are susceptible to cancers and RA.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of predicting those who are susceptible to cancers and rheumatoid arthritis. Since the activity is based on determining the patient population that is susceptible to cancers and RS, the predictability in the art is low. This is due to the fact that the art has recognized the

difficulty in determining the patient population who are susceptible to Alzheimer's disease.

The claims do not identify the patient population, therefore, the claims imply that anyone can be protected against cancers and rheumatoid arthritis. However, the Applicant has not shown who will be susceptible cancers and rheumatoid arthritis. There are too many variables between the experimentation, thus, it clearly shows the unpredictability of the art.

(5) The breadth of the claims:

The claims are drawn to a method for preventing or treating cancers or chronic rheumatoid arthritis, comprising administering pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a peptide. The claims do not identify patient population, so they imply that all everyone can be prevented from cancers and chronic rheumatoid arthritis.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

Although the specification provides guidance on how to measure the inhibition of the migration of T-cell derived leukemia cell in vitro, it does not provide guidance as when to administer the peptide composition in order to prevent RA. Example 5 discloses the use of human cell-derived leukemia SUP-T1 cells and 4F-benzoyl-TN-14003 peptide antagonist. Example 5 indicates that movement of T-cells are inhibited at low concentrations of 4F-benzoyl-TN-14003. This may be considered useful as an inhibitory

drug for chronic RA (see Example 5). Example 6 discloses the inhibitory activity of 4F-benzoyl-TN-14003 against breast cancer migration, and Example 7 discloses the anti-metastatic activity of 4F-benzoyl-TN-14003. These experiments are performed on cancerous cells and tissues, performed in *in vitro*. Example 9 discloses the effects of 4F-benzoyl-TN-14003 on mouse delayed-type hypersensitivity reaction utilizing preserved blood of sheep, and Example 10 discloses the therapeutic effects of 4F-benzoyl-TN-14003 on mouse collagen-induced arthritis. Example 10 discloses the injection of collagen into the base of the tail DBA/1JN mouse to induce arthritis. Example 10 further discloses that 4F-benzoyl-TN-14003 exhibited significant inhibitory activity against hindlimb swelling, arthritis score and body weight loss (see Example 10). The specification does not disclose how to prevent cancers and RA. The specification discloses the treatment of cancerous cells and RA already formed in the body. Additionally, it is unclear as to when to administer the compound is to be administered and the patient population. The working examples are directed towards the cancerous tissue or cell samples and blood samples. As stated above, the specification does not disclose how to prevent cancers and RA. The working examples are limited to cancerous tissues and cells and RA already formed in the body.

As described supra, the Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often

possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting, neuropathy, nausea, anorexia, seizures, hypocalcaemia, hyperuricemia, or obstruction...Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis).

Furthermore, arts indicate the difficulties in going from *in vitro* to *in vivo* for drug development for treatment of cancers. Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants...*In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test sites are not typical of the *in vivo* reality (see p. 167, left column, 1st paragraph). Gura T (Science, 1997, 278(5340): 1041-1042, encloses 1-5) indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (see p. 1, 2nd paragraph). Furthermore, Gura T indicates that the results of xenograft screening turned out to be not much better than those obtained with the original models,

mainly because the xenograft rumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues, for example (see p. 2, 4th paragraph). Further, when patient's tumor cells in Petri dishes or culture flasks and monitor the cells' responses to various anticancer treatments, they don't work because the cells simply fail to divide in culture, and the results cannot tell a researcher how anticancer drugs will act in the body (see p. 3, 7th paragraph). Furthermore, Jain RK (Scientific American, July 1994,58-65) indicates that the existing pharmacopoeia has not markedly reduced the number of deaths caused by the most common solid tumors in adults, among them cancers of the lung, breast, colon, rectum, prostate and brain (see p. 58, left most column, 1st paragraph). Further, Jain RK indicates that to eradicate tumors, the therapeutic agents must then disperse throughout the growths in concentrations high enough to eliminate every deadly cells...solid cancers frequently impose formidable barriers to such dispersion (see p. 58, bottom of the left most column continuing onto the top of the middle column). Jain RK indicates that there are 3 critical tasks that drugs must do to attack malignant cells in a tumor: 1) it has to make its way into a microscopic blood vessel lying near malignant cells in the tumor, 2) exit from the vessel into the surrounding matrix, and 3) migrate through the matrix to the cells. Unfortunately, tumors often develop in ways that hinder each of these steps (see p. 58, bottom of right most column). Thus, the art recognizes that going from *in vitro* studies to *in vivo* studies for cancer drug developments are difficult to achieve.

In regards to "a method for preventing or treating chronic rheumatoid arthritis", The Merck manual indicates that rheumatoid arthritis (RA) is a chronic autoimmune

disease producing damage mediated by cytokines, chemokines, and metalloproteases. Peripheral joints are symmetrically inflamed, often resulting in progressive destruction of articular structures. Diagnosis requires specific clinical, laboratory, and radiologic criteria. Treatment involves drugs, physical measures, and sometimes surgery (see Merck manual, Rheumatoid Arthritis). Further, the Merck manual indicates that although RA involves autoimmune reactions, the precise cause is unknown, many factors may contribute, such as genetic predisposition, unknown environmental factors (e.g., viral infections) and cigarette smoking (see Merck manual, RA, Etiology and Pathophysiology). Further, the Merck manual indicates that the onset of symptoms is usually insidious, beginning with systemic symptoms and progressing to joint symptoms, but symptoms can occur simultaneously (see Merck manual, RA, 1st paragraph, Symptoms and Signs). For diagnosis, patients should have a RF test, hand and wrist x-rays, and baseline x-rays of affected joints to document future erosive changes (see Merck manual, RA, 1st paragraph, Diagnosis). Furthermore, the Merck manual indicates that treatment involves a balance of rest and exercise, adequate nutrition, physical measures, drugs, and sometimes surgery. Drugs used are to reduce inflammation as means of preventing erosions and progressive deformity. Many promising new drugs that appear to slow the progression of RA are available (see Merck manual, RA, Treatment and Drugs for RA).

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against cancers and RA. There is no clear guidance as to how to determine the patient population, since cancer is an unregulated

proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age, and it is unclear who would develop cancers and RA, more guidance is necessary. Since the prior art is still unclear as to who are susceptible to cancers and RA, more guidance is necessary.

(8) The quantity of experimentation necessary:

Since it is uncertain to predict the patient population who are susceptible for cancers and rheumatoid arthritis, and the Applicant have not provided the appropriate time frame at which the compound should be administered, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the CXCR4 antagonist peptides would be effective in preventing cancers and rheumatoid arthritis.

Please note that the term "prevent" in an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat" or "alleviate", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes)- including preventing such disorders as cancers and rheumatoid arthritis, which is clearly not recognized in the medical art as being totally preventable condition.

New Matter Rejection-35 U.S.C. § 112, 1st

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 15, 17, 18, 23-24 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

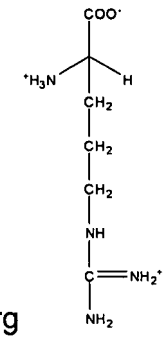
8. The claims are drawn to "a peptide according to formula (I) or a salt thereof wherein amino acid positions are numbered 1-14...A1 is an Arg, Lys, Orn, Cit, Ala, or Glu which is derivatized at the alpha-amino nitrogen with a substituted benzoyl group or A1 is absent..." The claims in question recite a "A1 is absent" and "alpha-amino nitrogen with a substituted benzoyl group".

Lack of Ipsis Verbis Support

9. The specification is void of any literal support for the "A1 is absent" and "alpha-amino nitrogen with a substituted benzoyl group" claimed. In the context of A1 of formula (I), the word "absent" is not present anywhere in the specification. The word "delete" is present in the specification in relation to A1 (see for example, paragraph [0012]). However, the word "delete" implies that A1 is present originally, and then deleted with a cleavage reaction. This is not in context of A1 being absent originally.

The phrase "alpha-amino nitrogen with a substituted benzoyl group" was not found in the specification. The word "nitrogen" was provided on at paragraph [0281] in relation to alkylating drug of the specification. The words "benzoyl group" was provided at paragraph [0056] in relation to N-terminal amino acid derivatization or non-derivatization of amino group. The only benzoyl group derivatives provided are fluorobenzoyl groups, 4F-benzoyl and 2F-benzyol (see paragraph [0056]). Throughout the specification, the only benzoyl groups provided are 4F-benzoyl and 2F-benzoyl (see for example, paragraph [0074], [0079], [0166] and so on). However, this is not in the context of "alpha-amino nitrogen".

Lack of Implicit or Inherent Support

10. "While there is not in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Thus support can be furnished implicitly or inherently for a specifically claimed limitation. However, the specification lacks any implicit or inherent support for the claimed "absent" in relation to A1 and "alpha-amino nitrogen with a substituted benzoyl group". As explained supra, there is no support for any concept of A1 being "absent" in the specification. The phrase "alpha-amino nitrogen with a substituted benzoyl group" can be interpreted as only the alpha-amino nitrogen being substituted with the benzoyl group. A1 can be Arg, Lys , Orn, Cit, Ala or Glu. Since Arg 

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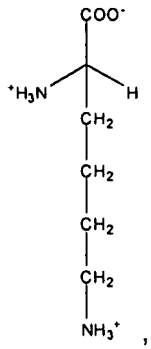
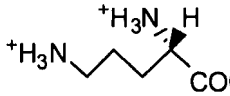
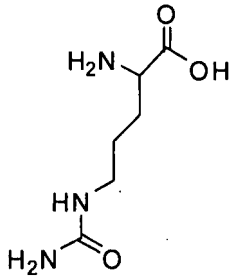
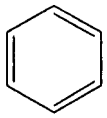
Lys  , Orn  , and Cit  have extra nitrogens in the amino acid, these can react with the benzoyl groups. Further, listing just the fluorbenzoyl groups 4F- and 2F-benzoyl does not encompass the vast number of benzoyl group moiety. Benzoyl groups can mean anything compound having  groups.

Rejection-35 U.S.C. 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> a. A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamamura et al (Biochemical and Biophysical Research Communications, 1998, 253: 877-882) in view of Fujii et al (WO 02/20561 translated into US Patent # 7138488).

15. The instant claims are drawn to a peptide according to formula (I) or a salt thereof, wherein amino acid positions are numbered 1-14 and each amino acid may be a D- or L-amino acid, and A1 is an R, K, O, C, A or E which is derivatized at the alpha-amino nitrogen with a substituted benzoyl group, or absent, A2 is R or E or derivatized at the alpha-amino nitrogen with a substituted benzoyl group if A1 is absent, A3 is an aromatic amino acid, A4, A5 is R, K, O, C, A or E, A6 is P, G, O, K, A, C, R or E, A7 is P, G, O, K, A, C or R, A8 is Y, F, A, Nal, C or E, A9 is R, K, O, C, A or E, A10 is C, E, R or K and A11 is R, E, K or C or a c-terminal derivative thereof.

15. Tamamura et al teach T140 having the sequence NH_2-R-R-Nal-C-Y-R-K-DK-P-Y-R-Cit-C-R-COOH (see Figure 1). This is a strong anti-HIV peptide T140 (see Title and abstract). This meets the sequence limitation of claims 1 and 2. The difference between the reference and the instant claims is that the reference does not teach alpha-amino nitrogen with a substituted benzoyl group.

16. However, Fujii N (US Patent '488) teaches polypeptides of A1-R-A2-C-Y-A3-A4-X-A5-A6-Cit-C-A7 or their salts (see abstract). The reference further teaches a sequence T140 that has the sequence H-R-R-Nal-C-Y-R-K-DK-P-Y-R-Cit-C-R-OH (see Table 1). Further, the reference teaches that the protected amino acid to be used for synthesis of the polypeptide means an amino acid whose functional group is protected by a protecting group according to the conventionally known method, and various kinds of protected amino acids are commercially available. Protecting group for an alpha-amino group of an amino acid is Boc, Fmoc, Tos, NO2, Mtr (benzenesulfonyl group), Pmc or Pbf (benzofuran-6-sulfonyl) (see column 6, lines 43-57). The reference further teaches that the polypeptide specifically binds to CXCR4 ligand (see column 1, lines 31-38).

17. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Tamamura et al and Fujii et al to produce a polypeptide having the same sequence with the N-terminal amino acid protected for synthesizing a polypeptide. One of ordinary skill in the art would be motivated to protect the N-terminal amino acid when synthesizing a polypeptide, since it is well known in the art, if there is a free amine, an amino acid may form a peptide bond to the other free amine, for example

ε amino group of Lysine. Fujii et al teach that a protected polypeptide having a desired amino acid sequence can be obtained (see column 7, lines 27-28). There is a reasonable expectation of success since both prior arts teach same polypeptide sequence that is utilized for the same purpose (anti HIV-1 peptide) and a protected polypeptide allows for a synthesis of desired amino acid sequence.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
Patent Examiner
AU 1654

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ANISH GUPTA
PRIMARY EXAMINER